Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Cantineau, Astrid E. P.; Cohlen, Ben J.; Heineman, Maas Jan

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[Intervention Review]

Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Astrid EP Cantineau[1], Ben J Cohlen[2], Maas Jan Heineman[3]

[1]Department of Obstetrics & Gynaecology , University Medical Centre, Groningen, Netherlands. [2]Department of Obstetrics & Gynaecology, Isala Clinics, Location Sophia, Zwolle, Netherlands. [3]Department of Obstetrics & Gynaecology Amsterdam Medical Centre, University of Amsterdam, Amsterdam, Netherlands

Contact address: Astrid EP Cantineau, Department of Obstetrics & Gynaecology , University Medical Centre, Slachthuisstraat 27, Groningen, 9713 MA, Netherlands. aepcantineau@gmail.com.

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ABSTRACT

Background

Controlled ovarian hyperstimulation (COH) combined with intrauterine insemination (IUI) is commonly offered to couples with subfertility that does not involve the fallopian tubes. Another method is fallopian tube sperm perfusion (FSP). This technique ensures the presence of higher sperm densities in the fallopian tubes at the time of ovulation than does standard IUI. The aim of this review was to determine whether FSP and IUI differ in improving the probability of conception.

Objectives

To investigate whether pregnancy and live birth outcomes differ between fallopian tube sperm perfusion and intrauterine insemination in the treatment of non-tubal subfertility.

Search methods

We searched the Menstrual Disorders and Subfertility Group Trials Register (October 2008), MEDLINE (January 1966 to October 2008), and EMBASE (January 1988 to October 2008). Abstracts of the American Society for Reproductive Medicine (1987 to 2008) and European Society for Human Reproduction and Embryology (1987 to 2008) meetings were searched using the same key or text words.

Selection criteria

Only truly randomised controlled studies comparing FSP with IUI were included in this review. Couples with non-tubal subfertility who have been trying to conceive for at least one year were included.

Data collection and analysis

Two review authors independently selected the trials for inclusion based on the quality of the studies.

Main results

Eight studies involving 595 couples were included in the meta-analysis. Only one study reported the live birth rate and there was no evidence of a difference between FSP and IUI (OR 1.2, 95% CI 0.39 to 3.5). There was no evidence of a difference between FSP and IUI for clinical pregnancy per couple (OR 1.2, 95% CI 0.79 to 1.7). A subgroup analysis which included couples with unexplained subfertility only (n = 239) did not report any difference between FSP and IUI (OR 1.6, 95% CI 0.89 to 2.8).

Authors' conclusions

For non-tubal subfertility, the results indicate no clear benefit for FSP over IUI. Therefore the advice offered to subfertile couples regarding the comparative use of FSP versus IUI in the treatment of non-tubal subfertility should reflect this.

PLAIN LANGUAGE SUMMARY

Intrauterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

It remains unclear whether fallopian tube sperm perfusion (FSP) is better than intrauterine insemination (IUI) for non-tubal infertility. Intrauterine insemination (IUI) is an assisted reproduction procedure that places sperm directly into the uterus. Fallopian tube sperm perfusion (FSP) is a similar procedure that places sperm into the woman's fallopian tube, closer to the eggs than IUI, in order to improve the chances of conception. Results of this review of randomised controlled trials indicate that it is unclear whether FSP leads to increased pregnancy rates compared to IUI in couples with non-tubal infertility. The type of catheter used to place sperm in the fallopian tube may be important.

(Synopsis prepared by Menstrual Disorders and Subfertility Review Group)

BACKGROUND

Description of the condition

Controlled ovarian hyperstimulation (COH) together with intrauterine insemination (IUI) is commonly offered to couples with subfertility factors not involving the fallopian tubes. Intrauterine insemination gained its popularity because it is simple, non-invasive, and a cost-effective technique (Hughes 1997).
Studies on the dynamics of sperm transport have shown that there is a progressive decline in the numbers of spermatozoa along the length of the female reproductive tract. In normal fallopian tubes a maximum of only 200 spermatozoa are present in the ampulla (Mamas 1996). Ripps 1994 showed that the number of spermatozoa in the pouch of Douglas was very low after IUI. However, the number of spermatozoa could be significantly increased with utero-tubal flushes. On the other hand, some authors state that there is no correlation between the number of spermatozoa inseminated and subsequent pregnancy rates if at least one to five million spermatozoa are inseminated (Dodson 1991; van Weert 2004). Taking these observations into consideration another simple non-invasive method was introduced, called fallopian tube sperm perfusion.

Description of the intervention

Fallopian tube sperm perfusion (FSP) is based on a pressure injection of 4 ml of sperm suspension while attempting to seal the cervix to prevent semen reflux. This ensures a sperm flushing of the fallopian tubes and an overflow of the inseminate into the pouch of Douglas (Fanchin 1995).

How the intervention might work

FSP was developed to ensure the presence of higher sperm densities in the fallopian tubes at the time of ovulation than provided with standard IUI.
However a possible disadvantages of FSP is the large volume of inseminate, which may flush the ova out of the tubes or induce abnormal myosalpingeal contractions resulting in expulsion of the ova from the tube and subsequent failure of fertilisation (Nuojua-Huttunen 1997).

Why it is important to do this review

A number of randomised controlled trials have been published that compare the efficacy of FSP with standard IUI. There were considerable variations in the results. Some of the studies did not have enough power to detect significant differences; therefore, it seemed appropriate to consider pooling the results. The aim of this review was to determine whether outcomes differ between FSP and IUI in improving the probability of conception. As one of the basic requirements for IUI, and subsequently FSP, is the presence of patent tubes we investigated the efficacy of FSP and IUI for the treatment of non-tubal subfertility.

OBJECTIVES

To investigate whether live birth rate and rate of ongoing pregnancy outcomes differ between fallopian tube sperm perfusion and intrauterine insemination in the treatment of non-tubal subfertility.

METHODS

Criteria for considering studies for this review

Types of studies

Only truly randomised controlled studies were included in this review. The method of allocation was assessed to determine whether each study was truly randomised or quasi-randomised.

Types of participants

(1) Couples who had been trying to conceive for at least one year.
(2) Male subfertility was defined as semen quality not meeting the criteria for normality as defined by the World Health Organization (WHO) in 1987. Thus, at least one of: sperm concentration < 20 x 10^6/ml, total motility < 50%, or normal morphology < 50%; < 14% was considered as abnormal when the Kruger criteria were used (Kruger 1993). In 1992 the WHO changed its criteria for sperm morphology from 50% to 30% (WHO 1992). Because many studies were performed before 1992, we used the 1987 definition of normality.
(3) Unexplained subfertility was defined as subfertility for at least one year without any abnormality found at a routine fertility check-up.
(4) The following characteristics of the participants were considered: age of the woman; duration of subfertility; ovulatory status confirmed with a biphasic basal body temperature chart (BBTC), luteal progesterone (P), or sonographic evidence of ovulation; tubal patency; and post-coital testing.

Types of interventions

Trials comparing FSP with IUI were considered with a special focus on:
(1) amount of semen injected;
(2) timing of insemination;
(3) use of a special device for FSP;
(4) method of ovarian stimulation;
(5) donor semen, or husband or partner semen.

Types of outcome measures

Studies were considered suitable for inclusion in the meta-analysis if they evaluated outcome measures that were relevant for determining the efficacy of fallopian sperm perfusion compared to intrauterine insemination, determined by:
(1) incidence of live births in both treated and control groups (live birth rate per woman);
(2) incidence of clinical pregnancies in both treated and control groups (pregnancy rate per woman);
(3) incidence of multiple pregnancies, ovarian hyperstimulation syndrome, spontaneous abortions, tubal pregnancies.

Search methods for identification of studies

See Appendix 1; Appendix 2; Appendix 3; Appendix 4.
We searched for all publications which described (or might have described) randomised controlled trials of fallopian tube sperm perfusion and intrauterine insemination in the treatment of non-tubal subfertility.
(1) We searched the Menstrual Disorders and Subfertility Group Trials Register for any trials (searched October 2008). See Review Group module for more details on the Specialised Register.
(2) We searched the following electronic databases:
MEDLINE (January 1966 to October 2008);
EMBASE search (1980 to October 2008).
These databases were searched using the Cochrane highly sensitive search string for randomised controlled trials and the following subject headings and keywords: artificial insemination; intrauterine; intra-uterine; homologous; IUI; AIH; fallopian; tube; sperm; perfusion; FSP.
(3) We handsearched the reference lists in all identified studies.
(4) Personal communication: we wrote letters to experts in the field, world wide.
(5) We handsearched abstracts of the American Society for Reproductive Medicine (1987 to 2008) and European Society for Human Reproduction and Embryology (1987 to 2008) meetings.
When important information was missing from the original publications we tried to contact the authors. Any additional information received was incorporated into this review.

Data collection and analysis

AEP Cantineau and MJ Heineman independently selected the trials to be included according to the above-mentioned criteria. Disagreements were resolved through arbitration by BJ Cohlen. Analysis of agreement between the two observers on inclusion of trials was performed using crude percentage agreement.
The type of study, participants, interventions, outcome measures, and the quality of all selected studies were extracted and assessed by the same two observers. The following factors were considered for each trial (and labelled: Yes, No, or Not stated).

Trial risk of bias

(1) Method of randomisation: truly randomised, quasi-randomised, or not stated? Where truly randomised was defined as using a centralised randomisation scheme or on-site computer system. Quasi-randomised trials (e.g. alternating record numbers, dates of birth, or odd and even numbers) were excluded. When the randomisation method was not stated, studies were placed in the 'waiting for assessment' category since some studies which claim to be randomised turn out to be not truly randomised (Dias 2006); further information was sought through e-mail and fax.

Concealment of allocation: adequate (e.g. by third party, sealed opaque envelopes) or inadequate (e.g. open list of random numbers, open envelopes, tables; or not clear (e.g. not stated, or stated without further description). In the latter case the review authors contacted the authors.

(2) What was the design of the study cross-over or parallel? Only the pre-crossover data of cross-over studies were included.

(3) Was the sample size determined using a prospective power calculation?

(4) Were details on dropouts (couples) given?

(5) Was the percentage of dropouts > 10%?

(6) Was the reason for cancelling cycles given?

(7) Was the percentage of cancelled cycles >10%?

Analyses of agreement, as mentioned above, were performed on the method of randomisation and study design.

Type of participants

(8) What was the duration of subfertility?

(9) Were prognostic factors such as age of the woman and duration of subfertility considered?

(10) Were female factors excluded or corrected? All women had to have regular menstrual cycles with biphasic body temperature charts or normal luteal progesterone; patent tubes on hysterosalpingography (HSG) or laparoscopy; no cervical factors, thus a positive post-coital test or normal cervical mucus with pH > 6.3 and Insler score > 11.

(11) Had treatments been applied previously? Was it tubal surgery, controlled ovarian hyperstimulation without insemination, or other?

Type of intervention

(12) What method of controlled ovarian hyperstimulation (COH) was used?

(13) Were criteria to cancel the insemination because of the risk of multiple pregnancies or ovarian hyperstimulation syndrome (cancellation criteria) described?

(14) Duration of treatment: how many treatment cycles were offered?

(15) How many inseminations were performed per cycle?

(16) What timing method was used in natural cycles: with luteinising hormone (LH) in blood or urine?

(17) What timing method was used in cycles with COH. When no GnRHa was used: was LH also measured in cycles with COH?

(18) What was the actual timing of IUI or FSP? Was IUI or FSP in natural cycles performed 20 to 40 hours after detecting the onset of the LH surge, and in cycles with COH 35 to 45 hours after hCG?

(19) Which semen was inseminated (donor semen or partner semen)?

(20) What method of semen preparation was applied?

(21) What were the semen characteristics before and after sperm processing (especially the number of motile spermatozoa that were inseminated)?

Type of outcome measures

Primary outcome

- The number of live births

Secondary outcomes

- The number of clinical pregnancies (total and ongoing) diagnosed by fetal heart beat
- The number of multiple pregnancies
- The miscarriage rate
- The number of cycles with ovarian hyperstimulation syndrome (OHSS)
- The number of tubal pregnancies

Analyses of agreement, using crude percentage agreement, were performed on the live birth rates, pregnancy rates (PR) per couple and per completed cycle.

The raw data were obtained from each study and summarised in a two-by-two table. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each individual trial using the Peto method.

An important part of a systematic review is a meta-analysis in which the results of similar randomised trials are pooled. The underlying assumption is that the differences found between these trials are likely to be differences in the extent of treatment effect rather than differences in the direction of treatment effect (Chalmers 1989). To test the hypothesis that the OR is constant across strata, several statistical methods have been developed. One way of doing this is to look at the graphical display of the 95% CIs of the individual trials (Alderson 2004). When these CIs do not overlap, the differences are likely to be statistically significant, thus the trials are heterogeneous. Statistically significant heterogeneity suggests that the observed differences in results of the individual trials are due to factors other than chance. In this case, one should be cautious about interpreting the estimated overall effect. To test for statistical heterogeneity we used the method of Breslow 1980. They proposed a test that sums up the squared deviations of observed and fitted values, each standardised by its variance. The statistics used follow an approximate Chi^2 distribution with N-1 degrees of freedom, N being the number of trials under study. However, when all trials included are of limited size (with large

95% CIs that are likely to overlap), the power to detect heterogeneity is relatively small and results should be interpreted cautiously. If the trials were statistically homogeneous, we pooled the data for each comparison and calculated the overall combined OR with 95% CI using the Peto method.

Although all trials might be statistically homogeneous, differences in clinical parameters are often considerable (clinical heterogeneity). These differences have to be taken into account when interpreting the pooled results. Clinical heterogeneity cannot be avoided because most centres use their own 'materials and methods'. On the other hand when all trials find similar results despite differences in clinical parameters, this strengthens the final conclusions. The Cochrane Handbook for Systematic Reviews of Interventions states: "There is nothing wrong with combining apples and oranges, if one is interested in fruit" (Alderson 2004). In the present review, when trials met the inclusion criteria and performed the same intervention but statistical heterogeneity was detected a random-effects model was used. The differences in participants, interventions, and outcome measures were addressed. When appropriate, subgroup analyses were performed by excluding those trials that used inadequate or completely different 'materials and methods' (for instance, different methods of COH).

Besides statistical and clinical heterogeneity, publication bias might also influence the interpretation of the pooled results. Publication bias, the phenomenon by which trials with positive results are more likely to be published (and thus identified) than trials with negative results, applies particularly to smaller trials (Begg 1989). A way to detect such a bias is to construct a funnel graph, plotting sample size versus effect size (Alderson 2004). In the absence of publication bias the graph is symmetrical.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

In the initial review, 27 studies were found using the adopted search strategy. All these studies were identified as potentially providing data that compared fallopian tube sperm perfusion with intrauterine insemination. Further investigation showed that 10 studies were adequate for inclusion in the review (three studies for sensitivity analysis only).

When updating the review, the search was again performed and six additional articles were found; one was eligible for inclusion. We also reviewed the original articles as part of the update and four studies (Gregoriou 1995; Kamel 1999; Papier 1998; Prietl 1999) did not state the exact randomisation method used. Neither did they report concealment of allocation, which made it questionable whether these articles were still suitable for inclusion in the meta-analysis without more detailed information (Dias 2006). Further information was requested using e-mail and fax and it was received.

Excluded studies

See the Characteristics of excluded studies table.

Twenty-one publications in total failed to meet the inclusion criteria because they either did not perform the comparison of interest or did not report a truly randomised trial design with adequate allocation concealment (Allahbadia 1998; Arroyo Vieyra 1995; Ciftci 1998; Desai 1998; Dodson 1998; Elhelw 2000; Fanchin 1996; Fanchin 1997; Kahn 1992; Kahn 1992a; Kahn 1993a; Karande 1995; Levitas 1999; Li 1993; Maheshwari 1998; Mamas 1996; Mamas 2006; Posada 2005; Prietl 1999; Soliman 2005; Soliman 1999).

Included studies

See the Characteristics of included studies table.

Eleven studies (Biacchiardi 2004; El Sadek 1998; Fanchin 1995; Filer 1996a; Gregoriou 1995; Kahn 1993; Ng 2003; Nuojua-Huttunen 1997; Papier 1998; Ricci 2001; Trout 1999) were included in this review and reviewed in detail. Two studies (Fanchin 1995; Filer 1996) were not included in the meta-analysis because only data per cycle were reported; or the separate first-cycle data of a cross-over study were not available. One publication (Trout 1999; Trout 1999 extended) was not included in the main meta-analysis but was included in the sensitivity analysis. Trout and co-workers extended the original study with a different group of patients with unexplained subfertility. The extended part of this trial has been treated as a separate trial and is listed as Trout 1999 extended in the tables and graphs. These studies appear in the table 'Characteristics of included studies' and were described in this review. We are still waiting further information on the duration of subfertility of the participants before this study can be included in the main analyses.

Studies awaiting assessment

See the table Characteristics of studies awaiting classification.

Two studies (Kamel 1999; Noci 2007) were placed in the awaiting further assessment category and not included in the updated review since insufficient details about randomisation and concealment of allocation could be obtained from the articles.

Attempts were made to contact the authors by e-mail and fax for details that were not reported and for more information about the published data. Eight replies have been received. The additional information from four authors resulted in inclusion of their studies and two studies were excluded (Biacchiardi 2004; Filer 1996a; Gregoriou 1995; Maheshwari 1998; Papier 1998; Prietl 1999).

Participants

Eight studies which reported on 595 women were included in the meta-analysis. The study (Trout 1999) included in the review for the sensitivity analysis only had an additional 269 women. Two studies were not included in the meta-analysis because they did not provide the number of women in each treatment arm (Fanchin 1995) or did not provide first cycle data (Filer 1996a). In all but two studies (El Sadek 1998; Gregoriou 1995), the duration

of subfertility was comparable at approximately 3.5 years (range 2.4 to 4.4 years). For the remaining two studies, Gregoriou 1995 reported a mean duration of subfertility of 6.5 and 6.3 years for each group, and the study of El Sadek 1998 reported a mean duration of subfertility of 7.3 and 8.6 years.

The age of the women was mentioned in all but two trials (Filer 1996a; Papier 1998), with a mean age (and standard deviation) of 31.2 years (3.7 years).

The types of subfertility included were: unexplained subfertility, male subfertility, mild endometriosis, ovarian dysfunction, cervical factor, and light peritubal adhesions. Low sperm count (< 10^6 sperm with progressive motility after migration) was one of the exclusion criteria in four studies (El Sadek 1998; Fanchin 1995; Kahn 1993; Ng 2003). No study mentioned previous fertility treatment or inclusion of people with secondary subfertility. Eight studies mentioned hysterosalpingography or laparoscopy to check tubal patency as a part of the fertility investigative work-up. Three studies (Fanchin 1995; Filer 1996; Papier 1998) did not give information on the investigative work-up.

Interventions

Four studies (El Sadek 1998; Nuojua-Huttunen 1997; Kahn 1993; Trout 1999) used clomiphene citrate (CC) alone or combined with human menopausal gonadotropin (hMG), followed by one dose of human chorionic gonadotropins (hCG). One study (Ricci 2001) used follicle stimulating hormone (FSH) as u-FSH and one study (Biacchiardi 2004) used r-FSH for ovarian stimulation followed by one dose of hCG. Three studies (Gregoriou 1995; Ng 2003; Papier 1998) stimulated with hMG alone followed by one dose of hCG when the leading follicle was > 18 mm in diameter. One study (Fanchin 1995) used three different stimulation protocols, in which CC, hMG, FSH, and gonadotropin releasing hormone agonist (GnRHa) were combined in different ways. Finally, one study (Filer 1996a) did not mention the type of controlled ovarian stimulation used.

The timing of insemination or perfusion was between 34 and 42 hours after hCG in all trials. All studies performed a single insemination for both groups. Two studies (Nuojua-Huttunen 1997; Papier 1998) did not mention the type of injected semen. The remaining studies used semen from the husband.

In seven studies (Fanchin 1995; Filer 1996a; Gregoriou 1995; Ng 2003; Nuojua-Huttunen 1997; Papier 1998; Trout 1999) the semen was prepared with the Percoll density gradient two-layer technique and four studies (Biacchiardi 2004; El Sadek 1998; Kahn 1993; Ricci 2001) used a swim-up technique to prepare the semen.

The volume of semen perfused for the FSP procedure was 4.0 ml in all but one study (Ng 2003) that inseminated a volume of 3.0 ml in the FSP group. For the IUI technique, the volumes of inseminated semen varied between 0.2 ml and 1.0 ml in the different studies. In five studies (El Sadek 1998; Fanchin 1995; Kahn 1993; Papier 1998; Ricci 2001) the Frydman catheter was used for the IUI procedure. The other studies used different types of catheters: Tomcat (Ng 2003), Kremer de la Fontaine (Biacchiardi 2004; Nuojua-Huttunen 1997), a Makler device (Gregoriou 1995), and a conventional IUI canula (Trout 1999). For the FSP procedure three studies (El Sadek 1998; Gregoriou 1995; Kahn 1993) used the Frydman catheter with an additional Allis clamp and two studies used the FAST system (Fanchin 1995; Ricci 2001). The other studies used a Foley catheter (Biacchiardi 2004; Nuojua-Huttunen 1997), an intrauterine injector with balloon (Ng 2003), a Makler cannula (Filer 1996a; Papier 1998), and a ZUII catheter with balloon (Trout 1999).

Four studies (Gregoriou 1995; Kahn 1993; Ng 2003; Ricci 2001) mentioned a maximum of three cycles per couple; one study (Biacchiardi 2004) reported a maximum of four cycles, and one study (Filer 1996a) six cycles per couple. The results of two studies (Nuojua-Huttunen 1997; Papier 1998) reported the same number of cycles as the number of included couples. The remaining studies (El Sadek 1998; Fanchin 1995; Trout 1999) did not mention a maximum number of cycles per couple.

Outcomes

One study reported the live birth rate (El Sadek 1998). Three studies reported ongoing pregnancies but no live birth rates (Fanchin 1995; Ng 2003; Ricci 2001). The remaining studies reported clinical pregnancy rates. All but one trial (Fanchin 1995) assessed clinical pregnancy rates per woman and all trials assessed clinical pregnancy rate per cycle.

Six studies included in the meta-analysis (El Sadek 1998; Fanchin 1995; Kahn 1993; Ng 2003; Nuojua-Huttunen 1997; Ricci 2001) reported on multiple pregnancy rates per treatment arm, and miscarriage rates were reported in five included studies (El Sadek 1998; Kahn 1993; Ng 2003; Nuojua-Huttunen 1997; Ricci 2001). Only one study (Fanchin 1995) reported the ovarian hyperstimulation syndrome (OHSS) rate per group. Two studies (Kahn 1993; Ricci 2001) reported the number of ectopic pregnancies. The study included for the sensitivity analysis only (Trout 1999) reported clinical pregnancy rates per couple and per cycle. Nuojua-Huttunen and co-workers did not mention the method of confirming pregnancy.

Risk of bias in included studies

See Figure 1; Figure 2.

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

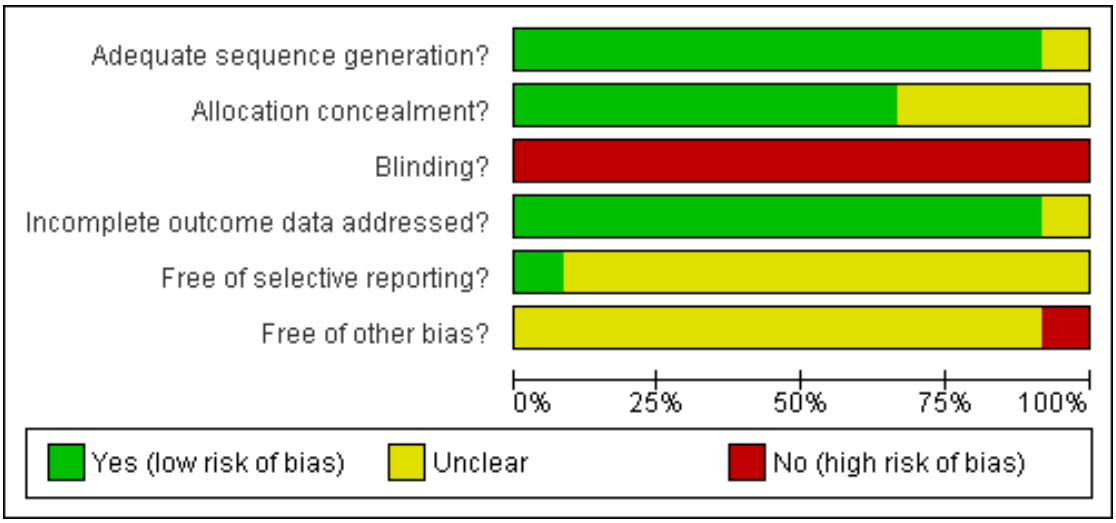
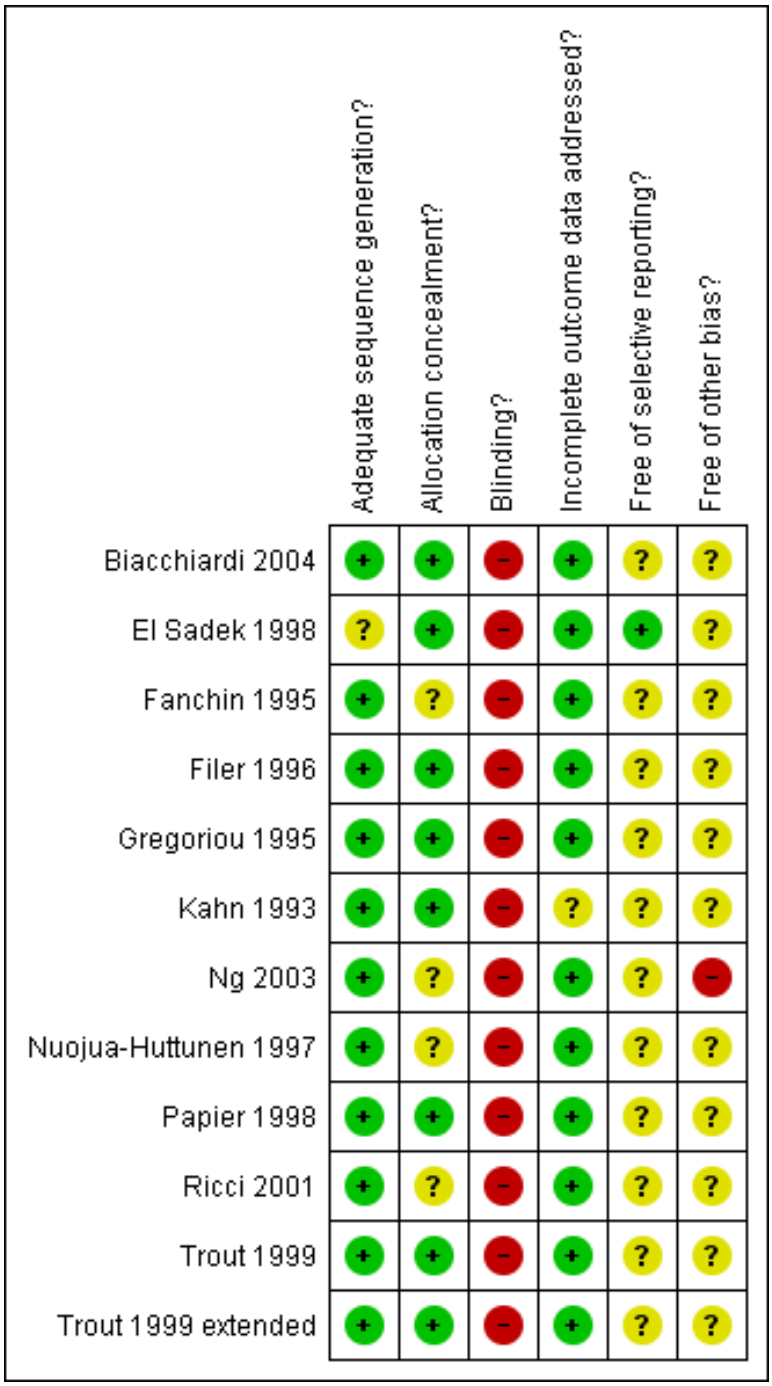


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Study design

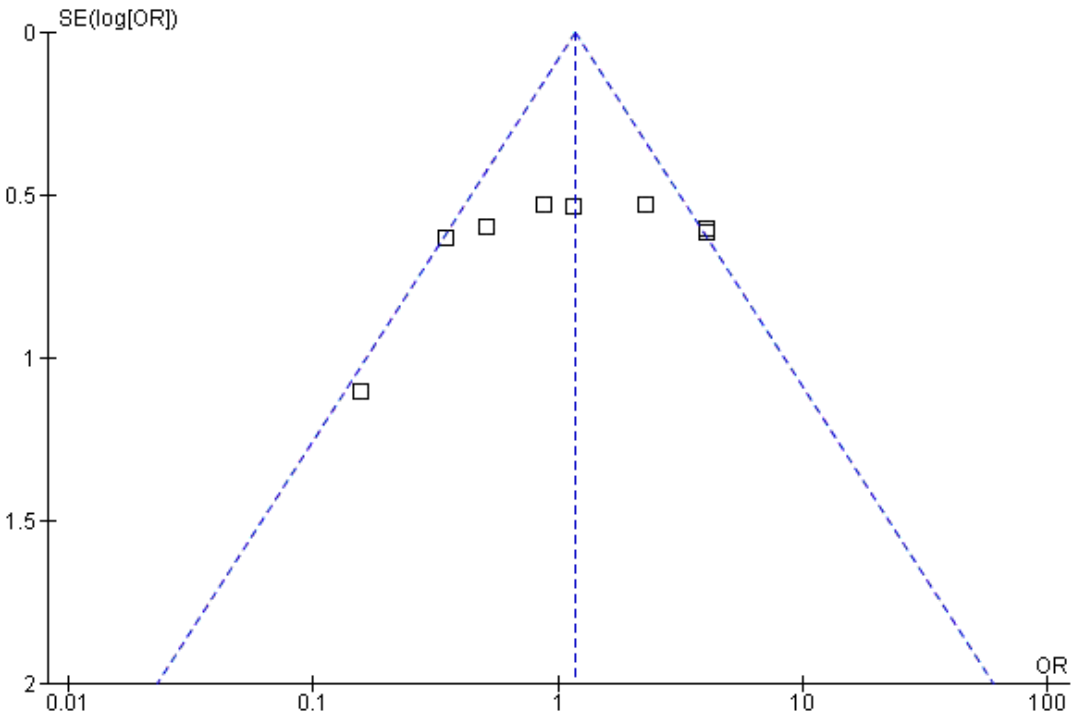
All but one included study (Biacchiardi 2004) had a parallel design. First-cycle data could be extracted from this study. All but one (Kahn 1993) were single-centre studies. The studies were performed in Egypt, France, Greece, Norway, Denmark, Finland, Argentina, Hongkong, Italy, and the USA.

Randomisation and concealment of allocation

All included studies had evidence of adequate randomisation procedures. The concealment of allocation was clearly stated in three studies (El Sadek 1998; Kahn 1993; Trout 1999). Additional information about randomisation and concealment of allocation was received through personal communication with Dr Papier and Dr Gregoriou resulting in inclusion of these trials.

A funnel plot of eight studies was symmetrical (Figure 3).

Figure 3. Funnel plot of comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion, outcome: 1.2 pregnancy rate per couple for non-tubal subfertility.



Blinding

Blinding was not reported in any of the studies.

Intention-to-treat

No study claimed to use an intention-to-treat analysis. Neither did any of the studies provide further information on whether participants really received the treatment to which they were randomised, in an adequate way, or whether they changed from one group to another.

Power calculation for sample size

Four studies (Ng 2003; Nuojua-Huttunen 1997; Ricci 2001; Trout 1999) performed power calculations for sample size. The study of Nuojua-Huttunen described a power calculation that assumed improvement of approximately 15% in favour of FSP over standard IUI as needing 100 couples; 100 couples were included and the trial reported no significant difference. Ng and co-workers stated that 60 (couples) in each arm were needed for a significant difference assuming that the pregnancy rate per cycle would be 25% per cycle for FSP and 10% per cycle for IUI; however, only 30 couples were included in each arm. The study of Trout and co-workers stated that 266 patients needed to be enrolled assuming a pregnancy rate of 15% for IUI and 30% for FSP. They included 268 cycles in total. Finally Ricci and co-workers carried out a power calculation based on previous studies; they used a pregnancy rate per cycle of 8% for IUI and 28% for FSP: 66 cycles per treatment arm would be necessary. Both groups contained 66 cycles and the trial reported no significant difference.

All items above are summarised in the 'Quality of included studies table'(Table 1).

Source of funding

No study reported funding from industry.

Effects of interventions

We identified 27 studies using the adopted search strategy. Overall, eight studies with a total of 595 couples were included in the meta-analysis comparing intrauterine insemination versus fallopian tube sperm perfusion for non-tubal subfertility. An analysis of agreement between the two review authors was performed for the method of randomisation and study design, which resulted in 96% agreement. Arbitration because of disagreement was necessary for one study.

Live birth rate per couple

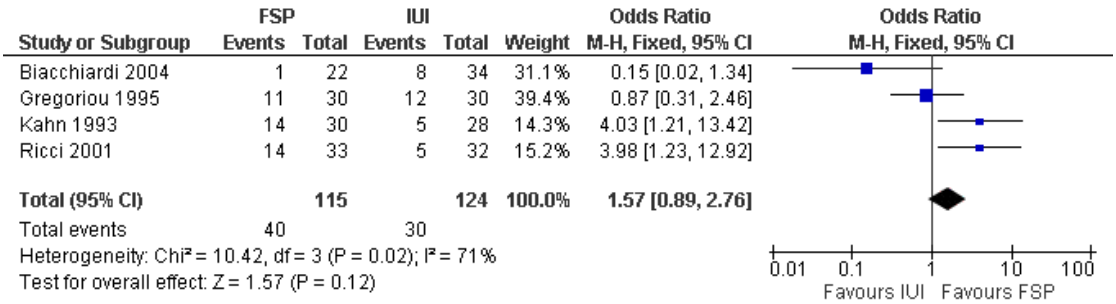
Only one study in the review (El Sadek 1998) reported the live birth rate per couple. There was no evidence of a difference between FSP and IUI (OR 1.17, 95% CI 0.39 to 3.53).

Pregnancy rate per couple

All but one study (Fanchin 1995) reported clinical pregnancy rates per couple. The meta-analysis reported a non-statistically significant higher clinical pregnancy rate with FSP (OR 1.2, 95% CI 0.79 to 1.7) compared with the IUI group using the fixed-effect model. Heterogeneity between the results of different studies was noted since the CIs did not overlap and the I^2 statistic for inconsistency was high (> 60%). To check the results a random-effects model was used. This gave a wider CI which also crossed the line of no significance (OR 1.1, 95% CI 0.56 to 2.3). Although the point estimate showed higher clinical pregnancy rates with FSP compared with IUI the CI showed that there was no evidence of a difference between FSP and IUI.

A subgroup analysis was made of studies which included couples with unexplained subfertility only (Biacchiardi 2004; Gregoriou 1995; Kahn 1993; Ricci 2001). This analysis revealed that couples suffering from unexplained subfertility did not benefit from FSP over IUI (OR 1.6, 95% CI 0.89 to 2.8), Figure 4. The I^2 statistic for inconsistency was high (67%); therefore, the random-effects model was used and also reporting no evidence of a difference between FSP and IUI (OR 1.5, 95% CI 0.44 to 5.0).

Figure 4. Forest plot of comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion, outcome: 1.3 Subgroup: pregnancy rate per couple for unexplained subfertility.



Multiple pregnancy rate per pregnancy

Five studies included in the meta-analysis reported on multiple pregnancy rates. The prevalence of twins, triplets, and quadruplets was not mentioned separately. There was no evidence of a difference between FSP and IUI (OR 1.6, 95% CI 0.51 to 4.8).

Miscarriage rate per pregnancy

Five studies reported the miscarriage rate per treatment group. The results indicated no evidence of a difference between FSP and IUI (OR 0.51, 95% CI 0.18 to 1.4)). The random-effects model was

used to check this result (OR 0.51, 95% CI 0.18 to 1.5) although the test for heterogeneity revealed statistical homogeneity.

Occurrence of ovarian hyperstimulation syndrome (OHSS)

Only one study in the meta-analysis (Fanchin 1995) reported on the occurrence of OHSS. There were no incidences reported in either group.

Ectopic pregnancy rate per pregnancy

Two studies reported the incidence of ectopic pregnancies: Kahn 1993 reported one ectopic pregnancy in the IUI group; and Ricci 2001 reported only one ectopic pregnancy which was in the FSP group. These results gave no evidence of a difference between FSP and IUI (OR 0.37, 95% CI 0.05 to 2.9).

Sensitivity analysis

The inclusion criteria of this review specified that the duration of subfertility had to be at least one year for study participants. In one study the duration of subfertility was not stated (Trout 1999; Trout 1999 extended). A sensitivity analysis was performed leaving out the duration of subfertility as a criterion so that these studies could be included. The pregnancy rate per couple changed from an OR of 1.2 (95% CI 0.79 to 1.7) to an OR of 1.4 (95% CI 0.98 to 1.9) for non-tubal subfertility. The outcome of pregnancy rate per couple changed from an OR of 1.6 (95% CI 0.89 to 2.8) to an OR of 1.9 (95% CI 1.2 to 3.2) for unexplained subfertility. However, the test for heterogeneity showed an I^2 higher than 60% so a random-effects model was used. The results were no longer statistically significant (OR 1.5, 95% CI 0.82 to 2.70), which indicates that the evidence is not very robust.

DISCUSSION

Summary of main results

The aim of this review was to investigate the effectiveness of fallopian tube sperm perfusion (FSP) compared to intrauterine insemination (IUI) with regard to pregnancy rates. The results from the trials included in this review indicate that use of FSP does not lead to higher live birth rates or clinical pregnancy rates than with IUI.

Overall completeness and applicability of evidence

A number of methodological considerations have to be taken into account when interpreting the results as there was significant heterogeneity between the results from the different trials included in the meta-analysis.

The types of subfertility differed among the trials. Each trial included unexplained subfertility but four studies also included other types of subfertility, such as mild male subfertility, ovarian dysfunction, cervical factor, light peritubal adhesions, and mild endometriosis (El Sadek 1998; Fanchin 1995; Ng 2003; Nuojua-Huttunen 1997). Subgroup analysis of trials that included couples with unexplained subfertility only suggested that in these couples FSP might have a small beneficial effect compared to IUI. However a random-effect model, which had to be used because of statistical heterogeneity, did not show a significant treatment effect in favour of FSP. It is known that severe male factor subfertility negatively influences the outcome of IUI (Cohlen 1998). It is unclear what effect other types of subfertility may have on the outcome for IUI or FSP. The question why IUI does not result in the same pregnancy rates for male subfertility remains unanswered.

The mean age of women in the different treatment groups was comparable. In most studies, women aged above 39 years was an exclusion criterion. One trial (Ricci 2001) did not state a maximum age for the women. Most fertility research centres have a maximum age for inclusion due to lower success rates with older women, mainly due to a lower ovarian reserve and oocyte quality in women above 40 years of age (Bukman 2000). The duration of subfertility was at least three years in all included studies. In one study (El Sadek 1998) the duration of subfertility was comparable between the IUI and FSP groups but when compared with the other studies the duration of subfertility was significantly longer. It is known that fertility treatment is less successful with longer duration of subfertility, however the pregnancy rates of El Sadek and co-workers were comparable with the other studies.

The method of controlled ovarian hyperstimulation varied among the included studies, which may have introduced clinical heterogeneity. Previous meta-analyses (Cantineau 2007; Crosignani 1996; Hughes 1997) concluded that gonadotropins are more effective than clomiphene citrate for treating subfertile couples in IUI programs. When the ovarian stimulation is more aggressive in one or more of the included studies, pregnancy rate per cycle will rise as well as rates of multiple pregnancies and OHSS. This should be taken into account when comparing study results. However, randomisation was done on the day of insemination, after the ovarian stimulation, which means it is impossible that the ovarian stimulation program influenced any difference between FSP and IUI outcomes.

Different methods were also used for sperm preparation, both the swim-up and Percoll gradient techniques. Use of a Percoll gradient might give a higher recovery rate (Cohlen 1998) although a Cochrane review on recovery rates after different semen analysis techniques concluded that no semen preparation technique is superior to another (Boomsma 2007).

Quality of the evidence

Finally, the methodological risk of bias of the included trials was similar. All of the trials were truly randomised. None of the trials used blinding. However, blinding would be methodologically difficult when comparing different insemination techniques and it is not likely that the outcomes are influenced by knowledge of the

procedure. An intention-to-treat analysis could not be performed because of insufficient data.

Potential biases in the review process

It is striking that the studies of Biacchiardi and Nuojua-Huttunen reported higher pregnancy rates with IUI after one cycle than other studies after three cycles with IUI (Kahn 1993; Ricci 2001). The power calculations performed for most studies assumed a pregnancy rate of 8% to 15% per cycle for IUI, based on available literature. This is lower than the results of Biacchiardi and Nuojua-Huttunen. The difference might be due to the type of catheter used, however direct evidence for this is lacking. The different types of catheters used for IUI have been compared but no study reported a significantly higher rate of pregnancy with any one of the catheters tested (Fancsovits 2005; Smith 2002; Vermeylen 2006).

Publication bias was unlikely as a funnel graph, plotting sample size versus effect size, was symmetrical seeFigure 3.

Agreements and disagreements with other studies or reviews

No other reviews comparing fallopian tube sperm perfusion with intrauterine insemination are known to the authors.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence that FSP results in higher pregnancy rates in couples suffering from non-tubal subfertility than with IUI. This conclusion is based on eight studies involving a total of 595 couples. As a result no advice can be given, based on the meta-analysis, on the optimal treatment of non-tubal subfertility. We advise, therefore, familiarity with one procedure since knowledge and routine use of one technique is possibly of more importance than the technique itself.

Implications for research

Large, randomised controlled trials should be performed comparing IUI and FSP:

- separately for unexplained subfertility and male subfertility, and using the same optimal stimulation protocol for each treatment group;

- with different types of catheters; and

- different types of semen preparation techniques.

When publishing the results, information about randomisation is essential. The number of ongoing pregnancies per couple or live birth rates per couple should be reported as well. Furthermore, the negative aspects of IUI and FSP, such as multiple pregnancies, ectopic pregnancies, and the incidence of ovarian hyperstimulation syndrome should be more carefully documented.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Biacchiardi 2004

Methods	Randomisation: blocked computer-generated sequence of numbers Trial design: cross-over Concealment of allocation: adequate
Participants	Participants: 56 women; 127 cycles Age of women: 33.2±4.3 years for the total group Duration of subfertility: total group 2.4±1.3 years Type of subfertility: unexplained subfertility
Interventions	Stimulation method: rFSH 75 IU from CD 3 Intervention: IUI or FSP 35-37 hours after hCG, with husband's semen Semen preparation: swim up Catheter used: IUI: Kremer dela fontaine FSP: Foley catheter Maximal number of cycles per couple: 4
Outcomes	PR/couple PR/cycle Multiple pregnancies OHSS rate Miscarriages
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated sequence of numbers blind to the operators
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

El Sadek 1998

Methods	Randomisation: block randomisation list Trial design: parallel Concealment of allocation: adequate
Participants	Participants: 96 women; 100 cycles Age of women: IUI 31.5±5.3; FSP 32.0±5.2 years Duration of subfertility: IUI 8.6±2.1; FSP 7.3±1.9 years Type of subfertility: male subfertility, unexplained subfertility, light peritubal adhesions, PCO, cervical hostility
Interventions	Stimulation method: CC or CC+hMG+hCG Intervention: IUI or FSP 34-36 hours after hCG, with husband's semen Semen preparation: swim up Catheter used: Frydman catheter (with Allis clamp for FSP) Maximal number of cycles per couple: not stated
Outcomes	LBR/women PR/couple PR/cycle Multiple pregnancies OHSS Miscarriage
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Blocked randomisation list
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Yes	
Free of other bias?	Unclear	Not stated

Fanchin 1995

Methods	Randomisation: block randomisation list Power analysis: not stated Trial design: parallel Concealment of allocation: not stated
Participants	Participants: 74 women; 100 cycles Age of women: IUI 31.8±4.6; FSP 31.8±3.7 years Duration of subfertility: IUI 3.6±1.2; FSP 3.4±1.1 years Type of subfertility: partial tube damage, idiopathic, cervical, ovulatory
Interventions	Stimulation method: 1) CC+hMG; 2) hMG alone; 3) FSH, hMG and GnRH agonist all followed by hCG Intervention: IUI or FSP 36 hours after hCG with husband's semen Sperm preparation: Percoll gradient Catheter used: Frydman catheter for IUI and FSP with FAST system Maximal number of cycles per couple: not stated
Outcomes	PR/cycle Multiple pregnancy Miscarriage rate OHSS rate
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Block randomisation list
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Filer 1996

Methods	Randomisation: computer-generated algorithm Power analysis: not stated Trial design: cross-over Concealment of allocation: adequate
Participants	Participants: 106 cycles Age of women: < 40 years IUI: FSP: Duration of subfertility: at least one year IUI: FSP: Type of subfertility: unexplained
Interventions	Stimulation method: not stated Intervention: IUI or FSP 36-42 hours after hCG Sperm preparation: Percoll gradient Catheter used: Makler cannula for IUI and FSP Maximal number of cycles per couple: 6
Outcomes	PR/cycle
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated algorithm
Allocation concealment?	Yes	After additional information from the author
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Gregoriou 1995

Methods	Randomisation: list of random numbers Trial design: parallel Concealment of allocation: adequate
Participants	Participants: 60 women; 150 cycles Age of women: IUI 30.4±3.5; FSP 30.3±3.6 years Duration of subfertility: IUI 6.5±2.1; FSP 6.3±2.5 years Type of subfertility: unexplained subfertility
Interventions	Stimulation method: hMG 75 IU from CD 3 Intervention: IUI or FSP 36 hours after hCG with husband's semen Sperm preparation: two layer Percoll gradient Catheter used: Makler device for IUI and Frydman catheter (with Allis clamp) for FSP Maximal number of cycles per couple: 3
Outcomes	PR/couple PR/cycle
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	List of random numbers
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Kahn 1993

Methods	Randomisation method: not stated Trial design: parallel Concealment of allocation: sealed envelopes Power analysis: not stated
Participants	Participants: 60 women; 103 cycles Age of women: IUI 31.8±0.8; FSP 31.7±0.6 years Duration of subfertility: > 3 years

Kahn 1993 (*Continued*)

	Type of subfertility: unexplained infertility
Interventions	Stimulation method: CC+hMG+hCG Intervention: IUI or FSP 34-37 hours after hCG with husband's semen semen preparation: swim up Catheter used: Frydman catheter (with Allis clamp for FSP) Maximal number of cycles per couple: 3
Outcomes	PR/cycle PR/woman Multiple pregnancy OHSS Miscarriage
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Unclear	Not stated
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Ng 2003

Methods	Randomisation method: computer-generated randomisation list Trial design: parallel Concealment of allocation: not stated Follow up: 3 cycles Power analysis: yes Intention-to-treat analysis: not performed
Participants	Participants: 90 women; 204 cycles 1) IUI 30 women, 68 cycles; 2) IUI 30 women, 76 cycles; and FSP 30 women, 59 cycles Age of women: 1) IUI 32.7±2.4; 2) IUI 32.9±2.7 years Duration of subfertility: 1) IUI 4.4±1.7; 2) IUI 4.2±2.1 years Type of subfertility: male, unexplained subfertility; and endometriosis

Ng 2003 (*Continued*)

Interventions	Stimulation method: 150 IU hMG from CD 3, dosage titrated later according to the ovarian response; 10.000 IU hCG 1) IUI 38 hours after hCG; 2) IUI 18 and 38 hours after hCG with husband's semen Sperm preparation: density gradient centrifugation method IUI procedure: 0.3-0.5 ml Tomcat catheter for IUI and intrauterine injectors (ZUOI-2) for FSP Maximal number of cycles per couple: 3
Outcomes	PR/couple PR/cycle Miscarriages Multiple pregnancy
Notes	Luteal support with 1500 IU hCG on day 5 and day 10 after hCG

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	No	Total motile sperm count in first insemination significantly different between IUI group and FSP group

Nuojua-Huttunen 1997

Methods	Randomisation: computer-generated random numbers Trial design: parallel Concealment of allocation: not stated Power analysis: yes
Participants	Participants: 100 women; 100 cycles Age of women: IUI 31.1±4.0; FSP 30.2±4.4 years Duration of subfertility: IUI 3.8±2.2; FSP 2.9±1.7 years Type of subfertility: male subfertility, unexplained subfertility, mild endometriosis, ovarian dysfunction

Nuojua-Huttunen 1997 (*Continued*)

Interventions	Stimulation method: CC+hMG+hCG Intervention: FSP or IUI 36 hours after hCG, type of semen not stated Semen preparation: Percoll gradient Catheter used: Kremer de la Fontaine for IUI; Foley catheter for FSP Maximal number of cycles per couple: 1
Outcomes	PR/cycle PR/woman Multiple pregnancies Miscarriage EUG OHSS
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Papier 1998

Methods	Randomisation: computer-generated random numbers Trial design: parallel Concealment of allocation: adequate Power analysis: no
Participants	Participants: 100 women; 87 cycles Age of women: not stated Duration of subfertility: at least one year Type of subfertility: mild male subfertility, unexplained subfertility

Papier 1998 (*Continued*)

Interventions	Stimulation method: hMG from CD 5+hCG Intervention: FSP 34 hours after hCG and IUI 38 hours after hCG; type of semen not stated Semen preparation: Percoll gradient Catheter used: Frydman for IUI; Makler cannula for FSP Maximal number of cycles per couple: 1
Outcomes	PR/cycle PR/woman
Notes	Luteal support with 400 mg progesterone

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Ricci 2001

Methods	Randomisation: random number generator on computer Trial design: parallel Concealment of allocation: not stated Power analysis: yes
Participants	Participants: 65 women; 132 cycles Age of women: IUI 34.8±4.6; FSP 35.5±3.5 years Duration of subfertility: IUI 3.5±1.4; FSP 3.4±1.3 years Type of subfertility: unexplained subfertility
Interventions	Stimulation method: u-hFSH+hCG Intervention: IUI and FSP 36 hours after hCG with husband's semen Semen preparation: swim up Catheter used: Frydman catheter for IUI; FAST system for FSP Maximal number of cycles per couple: 3

Ricci 2001 (*Continued*)

Outcomes	Ongoing PR/woman PR/cycle Multiple pregnancy OHSS
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number generator on computer
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Trout 1999

Methods	Randomisation: random number generator Trial design: parallel Concealment of allocation: third party Power analysis: yes
Participants	Participants: 268 women; 268 cycles Age of women: IUI 33.0±2.7; FSP 33.0±2.5 years Duration of subfertility: not stated Type of subfertility: ovulation dysfunction, unexplained infertility, male factor, endometriosis, cervical mucus factor, multiple diagnosis
Interventions	Stimulation method: CC+gonadotropins or gonadotropins alone+hCG Intervention: IUI or FSP 36 hours after hCG with husband's semen Semen preparation: Percoll gradient Catheter used: IUI catheter for IUI; ZUI II catheter for FSP Maximal number of cycles per couple: not stated
Outcomes	PR/woman PR/cycle Ectopic pregnancy

Trout 1999 (*Continued*)

Notes	Duration of infertility unknown	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Random number generator
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

Trout 1999 extended

Methods	Randomisation: random number generator Trial design: parallel Concealment of allocation: adequate	
Participants	Participants: 101 women; 101 cycles Age of women: not stated Duration of subfertility: not stated Type of subfertility: unexplained subfertility	
Interventions	Stimulation method: CC+gonadotropins or gonadotropins alone+hCG Intervention: IUI or FSP 36 hours after hCG with husband's semen Semen preparation: Percoll gradient Catheter used: IUI catheter for IUI; ZUI II catheter for FSP Maximal number of cycles per couple: not stated	
Outcomes	PR/woman PR/cycle	
Notes	Duration of infertility unknown; the study was extended only for patients with unexplained subfertility	
Risk of bias		
Item	**Authors' judgement**	**Description**

Trout 1999 extended (*Continued*)

Adequate sequence generation?	Yes	Random number generator
Allocation concealment?	Yes	A - Adequate
Blinding? All outcomes	No	
Incomplete outcome data addressed? All outcomes	Yes	
Free of selective reporting?	Unclear	Not stated
Free of other bias?	Unclear	Not stated

CC = clomiphene citrate
FSH = follicle stimulating hormone
FSP = fallopian sperm perfusion
GnRH = gonadotropin-releasing hormone
hMG = human menopausal gonadoropin
IUI = Intrauterine insemination
LBR = live birth rate
OHSS = ovarian hyperstimulation syndrome
PR = pregnancy rate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allahbadia 1998	Randomisation method was not stated, and the groups were not equal (369 in IUI group and 20 in FSP group), which makes adequate randomisation impossible. The author did not reply to our request for further information. Duration of subfertility was not stated
Arroyo Vieyra 1995	Randomisation method was not stated, and the groups were not equal (95 cycles with IUI and 36 cycles with FSP), which makes adequate randomisation improbable. The author did not reply to our request for further information
Ciftci 1998	The trial was quasi-randomised. The duration of subfertility was not stated. The author gave additional information regarding data after the first cycle. However this data was only pregnancies per cycle. Moreover there were no data available on the duration of subfertility
Desai 1998	Randomisation method was not stated, but the groups were not equal (369 in IUI group and 20 in FSP group), which makes adequate randomisation improbable. The author did not reply to our request for further information. The duration of subfertility was not stated

(*Continued*)

Dodson 1998	The trial did not perform the comparison of interest.
Elhelw 2000	Letter. Publication did not perform the comparison of interest.
Fanchin 1996	Letter. Publication did not perform the comparison of interest.
Fanchin 1997	Letter. Publication did not perform the comparison of interest.
Kahn 1992	Cohort study.
Kahn 1992a	Cohort study.
Kahn 1993a	This study did not perform the comparison of interest.
Karande 1995	Both IUI and FSP were performed on two consecutive days after hCG administration. A substantial number of women with tubal subfertility were included. The duration of subfertility was not stated
Levitas 1999	This study did not perform the comparison of interest.
Li 1993	Case report which described a simple non-invasive method of Fallopian tube sperm perfusion. This study did not perform the comparison of interest
Maheshwari 1998	The trial was quasi-randomised.
Mamas 1996	The trial was quasi-randomised.
Mamas 2006	The trial did not perform the comparison of interest. Intrauterine tuboperitoneal insemination is not the same as fallopian tube sperm perfusion
Posada 2005	The trial did not perform the comparison of interest.
Prietl 1999	This study compared conventional IUI with intratubal insemination which is different from perfusion of the fallopian tubes (FSP)
Soliman 1999	The trial was a non-controlled randomised trial.
Soliman 2005	The trial did not perform the comparison of interest.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kamel 1999

Methods	Randomised cross-over study
Participants	120 couples
Interventions	IUI versus FSP
Outcomes	Pregnancy
Notes	Allocation not clear, first-cycle data available

Noci 2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	

DATA AND ANALYSES

Comparison 1. Intrauterine insemination versus fallopian tube sperm perfusion

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 life birth rate per couple	1	96	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.39, 3.53]
2 pregnancy rate per couple for non tubal subfertility	8	595	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [0.79, 1.71]
3 Subgroup: pregnancy rate per couple for unexplained subfertility	4	239	Odds Ratio (M-H, Fixed, 95% CI)	1.57 [0.89, 2.76]
4 multiple pregnancy rate	5	97	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.51, 4.76]
5 miscarriage rate	5	183	Odds Ratio (M-H, Fixed, 95% CI)	0.51 [0.18, 1.44]
6 ectopic pregnancy	2	38	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.05, 2.88]
7 Sensitivity analysis: pregnancy rate per couple for non tubal subfertility (any duration of infertility)	10	964	Odds Ratio (M-H, Fixed, 95% CI)	1.35 [0.98, 1.87]
8 Sensitivity analysis: pregnancy rate per couple for unexplained subfertility (any duration of infertility)	5	340	Odds Ratio (M-H, Fixed, 95% CI)	1.92 [1.16, 3.17]

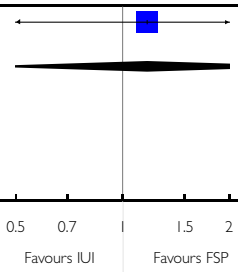
Analysis 1.1. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 1 life birth rate per couple.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 1 life birth rate per couple

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
El Sadek 1998	8/48	7/48		100.0 %	1.17 [0.39, 3.53]
Total (95% CI)	**48**	**48**		**100.0 %**	**1.17 [0.39, 3.53]**
Total events: 8 (FSP), 7 (IUI)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.28 (P = 0.78)					



Analysis 1.2. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 2 pregnancy rate per couple for non tubal subfertility.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

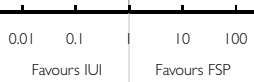
Outcome: 2 pregnancy rate per couple for non tubal subfertility

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Biacchiardi 2004	1/22	8/34		12.5 %	0.15 [0.02, 1.34]
El Sadek 1998	9/48	8/48		13.6 %	1.15 [0.40, 3.30]
Gregoriou 1995	11/30	12/30		15.9 %	0.87 [0.31, 2.46]
Kahn 1993	14/30	5/28		5.8 %	4.03 [1.21, 13.42]
Ng 2003	17/30	11/30		10.0 %	2.26 [0.80, 6.36]
Nuojua-Huttunen 1997	4/50	10/50		19.2 %	0.35 [0.10, 1.20]
Papier 1998	5/50	9/50		16.9 %	0.51 [0.16, 1.63]
Ricci 2001	14/33	5/32		6.1 %	3.98 [1.23, 12.92]
Total (95% CI)	**293**	**302**		**100.0 %**	**1.17 [0.79, 1.71]**

Total events: 75 (FSP), 68 (IUI)

Heterogeneity: Chi^2 = 19.11, df = 7 (P = 0.01); I^2 =63%

Test for overall effect: Z = 0.79 (P = 0.43)



Analysis 1.3. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 3 Subgroup: pregnancy rate per couple for unexplained subfertility.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 3 Subgroup: pregnancy rate per couple for unexplained subfertility

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Biacchiardi 2004	1/22	8/34		31.1 %	0.15 [0.02, 1.34]
Gregoriou 1995	11/30	12/30		39.4 %	0.87 [0.31, 2.46]
Kahn 1993	14/30	5/28		14.3 %	4.03 [1.21, 13.42]
Ricci 2001	14/33	5/32		15.2 %	3.98 [1.23, 12.92]
Total (95% CI)	**115**	**124**		**100.0 %**	**1.57 [0.89, 2.76]**
Total events: 40 (FSP), 30 (IUI)					
Heterogeneity: Chi^2 = 10.42, df = 3 (P = 0.02); I^2 =71%					
Test for overall effect: Z = 1.57 (P = 0.12)					

Analysis 1.4. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 4 multiple pregnancy rate.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 4 multiple pregnancy rate

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
El Sadek 1998	2/9	1/8		16.0 %	2.00 [0.15, 27.45]
Kahn 1993	2/14	0/5		11.6 %	2.20 [0.09, 53.85]
Ng 2003	5/17	2/11		33.4 %	1.88 [0.29, 11.97]
Nuojua-Huttunen 1997	0/4	1/10		16.4 %	0.70 [0.02, 20.91]
Ricci 2001	3/14	1/5		22.6 %	1.09 [0.09, 13.78]
Total (95% CI)	**58**	**39**		**100.0 %**	**1.56 [0.51, 4.76]**

Total events: 12 (FSP), 5 (IUI)

Heterogeneity: Chi^2 = 0.40, df = 4 (P = 0.98); I^2 =0.0%

Test for overall effect: Z = 0.79 (P = 0.43)

Analysis 1.5. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 5 miscarriage rate.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 5 miscarriage rate

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
El Sadek 1998	1/9	1/8		9.6 %	0.88 [0.05, 16.74]
Kahn 1993	2/14	1/5		12.9 %	0.67 [0.05, 9.47]
Ng 2003	2/17	4/11		43.8 %	0.23 [0.03, 1.59]
Nuojua-Huttunen 1997	2/50	2/50		19.6 %	1.00 [0.14, 7.39]
Ricci 2001	1/14	1/5		14.0 %	0.31 [0.02, 6.12]
Total (95% CI)	**104**	**79**		**100.0 %**	**0.51 [0.18, 1.44]**

Total events: 8 (FSP), 9 (IUI)

Heterogeneity: Chi^2 = 1.35, df = 4 (P = 0.85); I^2 =0.0%

Test for overall effect: Z = 1.27 (P = 0.21)

Analysis 1.6. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 6 ectopic pregnancy.

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 6 ectopic pregnancy

Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Kahn 1993	0/14	1/5		76.3 %	0.10 [0.00, 3.01]
Ricci 2001	1/14	0/5		23.7 %	1.22 [0.04, 34.86]
Total (95% CI)	**28**	**10**		**100.0 %**	**0.37 [0.05, 2.88]**
Total events: 1 (FSP), 1 (IUI)					
Heterogeneity: Chi^2 = 1.04, df = 1 (P = 0.31); I^2 =4%					
Test for overall effect: Z = 0.95 (P = 0.34)					

Analysis 1.7. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 7 Sensitivity analysis: pregnancy rate per couple for non tubal subfertility (any duration of infertility).

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 7 Sensitivity analysis: pregnancy rate per couple for non tubal subfertility (any duration of infertility)

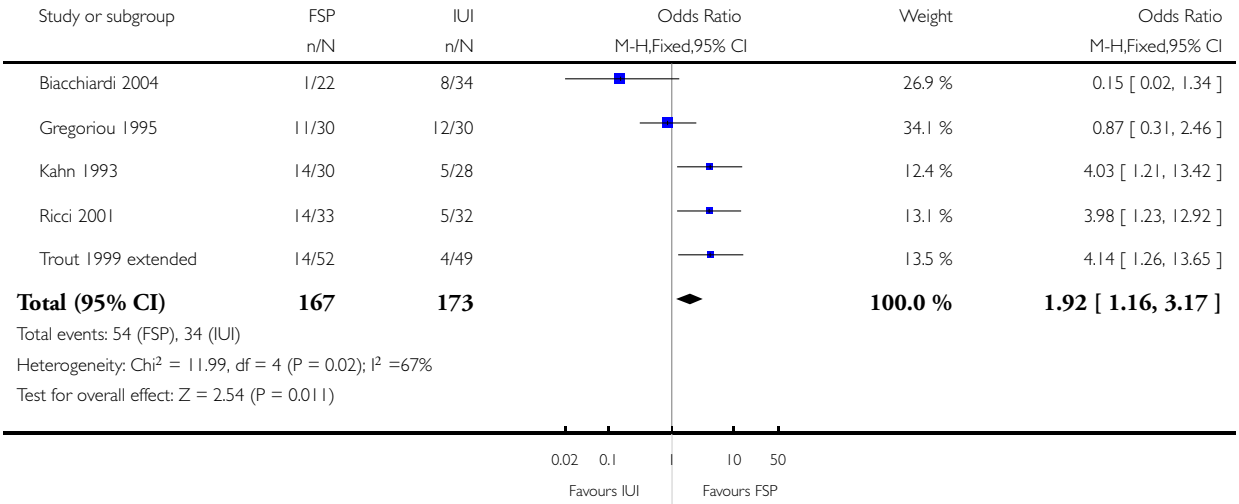
Study or subgroup	FSP n/N	IUI n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Biacchiardi 2004	1/22	8/34		9.6 %	0.15 [0.02, 1.34]
El Sadek 1998	9/48	8/48		10.4 %	1.15 [0.40, 3.30]
Gregoriou 1995	11/30	12/30		12.1 %	0.87 [0.31, 2.46]
Kahn 1993	14/30	5/28		4.4 %	4.03 [1.21, 13.42]
Ng 2003	17/30	11/30		7.6 %	2.26 [0.80, 6.36]
Nuojua-Huttunen 1997	4/50	10/50		14.7 %	0.35 [0.10, 1.20]
Papier 1998	5/50	9/50		12.9 %	0.51 [0.16, 1.63]
Ricci 2001	14/33	5/32		4.7 %	3.98 [1.23, 12.92]
Trout 1999	18/131	14/137		18.8 %	1.40 [0.67, 2.94]
Trout 1999 extended	14/52	4/49		4.8 %	4.14 [1.26, 13.65]
Total (95% CI)	**476**	**488**		**100.0 %**	**1.35 [0.98, 1.87]**
Total events: 107 (FSP), 86 (IUI)					
Heterogeneity: Chi^2 = 22.73, df = 9 (P = 0.01); I^2 =60%					
Test for overall effect: Z = 1.83 (P = 0.068)					

Analysis 1.8. Comparison 1 Intrauterine insemination versus fallopian tube sperm perfusion, Outcome 8 Sensitivity analysis: pregnancy rate per couple for unexplained subfertility (any duration of infertility).

Review: Intra-uterine insemination versus fallopian tube sperm perfusion for non-tubal infertility

Comparison: 1 Intrauterine insemination versus fallopian tube sperm perfusion

Outcome: 8 Sensitivity analysis: pregnancy rate per couple for unexplained subfertility (any duration of infertility)



ADDITIONAL TABLES

Table 1. Quality of included studies

Study	randomisation	allocation	power calculation	intention to treat	blinding
Biacchiardi	computer-generated randomisation list	not clear	not stated	none stated	none
El Sadek	blocked randomisation list	adequate	not stated	none stated	none
Fanchin	blocked randomisation list	not stated	not stated	none stated	none
Kahn	sealed envelopes	adequate	not stated	none stated	none
Ng	computer-generated randomisation list	not stated	performed	none stated	none

Table 1. Quality of included studies (*Continued*)

Nuojua-Huttunen	computer-generated random numbers	not stated	performed	none stated	none
Ricci	ran-dom number gener-ator on computer	not stated	performed	none stated	none
Trout	ran-dom number gener-ator on computer	adequate	performed	none stated	none

APPENDICES

Appendix 1. MEDLINE

1 Insemination, Artificial/ (6821)
2 (intrauter$ adj5 inseminat$).tw. (1194)
3 (intra-uter$ adj5 inseminat$).tw. (131)
4 IUI.tw. (703)
5 or/1-4 (7614)
6 fallopian tube sperm perfusion.tw. (19)
7 FSP.tw. (446)
8 (Fallopian adj5 sperm$).tw. (97)
9 (tub$ adj5 sperm$).tw. (1868)
10 sperm$ flush$.tw. (7)
11 or/6-10 (2326)
12 5 and 11 (80)
13 randomised controlled trial.pt. (234274)
14 controlled clinical trial.pt. (74820)
15 Randomized Controlled Trials/ (48327)
16 Random allocation/ (57750)
17 Double-blind method/ (91028)
18 Single-blind method/ (10880)
19 or/13-18 (397294)
20 clinical trial.pt. (435392)
21 exp clinical trials/ (190560)
22 (clin$ adj25 trial$).ti,ab,sh. (129372)
23 ((singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).ti,ab,sh. (90362)
24 Placebos/ (26128)
25 placebo$.ti,ab,sh. (114490)
26 random$.ti,ab,sh. (490003)
27 Research design/ (47276)
28 or/20-27 (866440)
29 animal/ not (human/ and animal/) (3095759)
30 19 or 28 (873731)

31 30 not 29 (800552)
32 12 and 31 (23)
33 (2003$ or 2004$ or 2005$ or 2006$ or 2007$).ed. (3111083)
34 32 and 33 (5)
35 from 34 keep 1-5 (5)

Appendix 2. CENTRAL

1 Insemination, Artificial/ (112)
2 (intrauter$ adj5 inseminat$).tw. (290)
3 (intra-uter$ adj5 inseminat$).tw. (22)
4 IUI.tw. (206)
5 or/1-4 (378)
6 fallopian tube sperm perfusion.tw. (21)
7 FSP.tw. (30)
8 (Fallopian adj5 sperm$).tw. (29)
9 (tub$ adj5 sperm$).tw. (47)
10 sperm$ flush$.tw. (0)
11 or/6-10 (70)
12 5 and 11 (30)
13 from 12 keep 1-30 (30)

Appendix 3. CINAHL

1 Insemination, Artificial/ (163)
2 (intrauter$ adj5 inseminat$).tw. (30)
3 (intra-uter$ adj5 inseminat$).tw. (4)
4 IUI.tw. (16)
5 or/1-4 (178)
6 fallopian tube sperm perfusion.tw. (2)
7 FSP.tw. (17)
8 (Fallopian adj5 sperm$).tw. (2)
9 (tub$ adj5 sperm$).tw. (7)
10 sperm$ flush$.tw. (0)
11 or/6-10 (22)
12 5 and 11 (2)
13 exp clinical trials/ (43714)
14 Clinical trial.pt. (20712)
15 (clinic$ adj trial$1).tw. (10227)
16 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$3 or mask$3)).tw. (6114)
17 Randomi?ed control$ trial$.tw. (8946)
18 Random assignment/ (15159)
19 Random$ allocat$.tw. (1023)
20 Placebo$.tw. (8559)
21 Placebos/ (3489)
22 Quantitative studies/ (3196)
23 Allocat$ random$.tw. (60)
24 or/13-23 (61301)
25 12 and 24 (2)
26 from 25 keep 1-2 (2)

Appendix 4. EMBASE

1 fallopian tube sperm perfusion.tw. (22)
2 FSP.tw. (345)
3 (Fallopian adj5 sperm$).tw. (80)
4 (tub$ adj5 sperm$).tw. (1383)
5 sperm$ flush$.tw. (5)
6 or/1-5 (1737)
7 exp Artificial Insemination/ (3671)
8 (intrauter$ adj5 inseminat$).tw. (1172)
9 (intra-uter$ adj5 inseminat$).tw. (129)
10 IUI.tw. (737)
11 or/7-10 (4753)
12 6 and 11 (74)
13 Controlled study/ or randomised controlled trial/ (2405316)
14 double blind procedure/ (63789)
15 single blind procedure/ (6559)
16 crossover procedure/ (18585)
17 drug comparison/ (81250)
18 placebo/ (97915)
19 random$.ti,ab,hw,tn,mf. (367123)
20 latin square.ti,ab,hw,tn,mf. (1064)
21 crossover.ti,ab,hw,tn,mf. (32554)
22 cross-over.ti,ab,hw,tn,mf. (11275)
23 placebo$.ti,ab,hw,tn,mf. (146355)
24 ((doubl$ or singl$ or tripl$ or trebl$) adj5 (blind$ or mask$)).ti,ab,hw,tn,mf. (106285)
25 (comparative adj5 trial$).ti,ab,hw,tn,mf. (5769)
26 (clinical adj5 trial$).ti,ab,hw,tn,mf. (483066)
27 or/13-26 (2886258)
28 nonhuman/ (2878264)
29 animal/ not (human/ and animal/) (12847)
30 or/28-29 (2881866)
31 27 not 30 (1695407)
32 12 and 31 (28)
33 (2003$ or 2004$ or 2005$ or 2006$ or 2007$).em. (2449289)
34 32 and 33 (6)
35 from 34 keep 1-6 (6)

WHAT'S NEW

Last assessed as up-to-date: 5 December 2007.

Date	Event	Description
11 February 2009	New citation required but conclusions have not changed	Review updated Dec 2007

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 3, 2004

Date	Event	Description
1 October 2008	New search has been performed	Search revised and re-run; new study added (Ng et al 2003) and two studies waiting for assessment
3 June 2008	Amended	Converted to new review format.
6 December 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

AE Cantineau did the literature search and selected relevant trials for inclusion in the review. She also performed the statistical analyses and wrote the bulk of the results and discussion section. She analysed articles for the update of the review and updated the review.

MJ Heineman was the second review author for selections of relevant trials for inclusion. For the update he analysed the selected articles. He also contributed to drafts of the review.

BJ Cohlen together with JH Evers and H Al-Inany took the lead in writing the original protocol for this review, was the third review author, and resolved any disagreements between the first two review authors. He also contributed to drafts of the review and contributed to the update of the review.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Isala Clinics, Zwolle, Netherlands.

visit congress meetings to present results of review

- The Cochrane Collaboration, New Zealand.

technical support

- University Medical Centre Groningen, Netherlands.

technical support

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Fallopian Tubes; *Pregnancy Outcome; *Reproductive Techniques, Assisted; *Sperm Count; Infertility, Female; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy